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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,043	FUSSENEGGER ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 9-28* is/are pending in the application.

4a) Of the above claim(s) *10-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02-15-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 08-29-2008 has been entered.
3. Status of claims. Claims 1-4 and 9-28 are pending. Claims 1, 2, 3, 4 and 9 have been amended, claims 5-8 have been canceled and claim 28 has been added by applicants' amendment filed on 08-29-2008. Claims 10-27 are withdrawn from consideration as being directed to non-elected invention pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim. Because applicant did not distinctly and specifically pointed out the supposed errors in the restriction requirement, the election was previously treated as an election **without traverse** (MPEP § 818.03(a)).
4. Therefore claims 1-4, 9 and 28 are currently being examined to which the following grounds of rejection are applicable.

Withdrawn objections/rejections in response to Applicant arguments or amendments.

Nucleotides and/or amino acid sequences. Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

In view of applicants' amendment of the specification at pages 7-8 to include the appropriate SEQ ID NOS. for the nucleotide sequences used as primers (e.g., forward and reverse primers) and further in view of applicants' submission of a sequence listing to include

the sequences identified as SEQ ID No. 1 and SEQ ID No. 2 in Applicants' reply filed on 08-29-2008, the notice of non compliance with the sequence rules under 37 C.F.R. 1.821- 1.825 has been withdrawn.

Note that Applicants have already submitted a sequence listing filed on 03-01-2006 comprising the sequences identified as SEQ ID No. 1 and SEQ ID No. 2, a copy of the "Sequence Listing" in computer readable form and a statement that the content of the paper and computer readable copies are the same.

Claim Objection

In view of Applicants' cancellation of the abbreviation "OP" in claims 1, 2, 3 and 4 , objection to claims 1, 3 and 4 because the phrase "OP operator-containing promoters" as recited in claim 1, subpart a, that was not consistent with the phrase "OP-containing promoters", as recited in claims 3, has been withdrawn.

In view of Applicants' amendment of claim 1, at line 2 of the claim to enclose in parenthesis the acronyms RTF, objection to claim 1 has been withdrawn.

Specification Objection

In view of Applicants' amendment of the disclosure at page 2, paragraph [005], to remove an embedded hyperlink and/or other form of browser-executable code, objection to the Specification has been withdrawn.

Claim Rejections - 35 USC § 101

In view of Applicants' amendment of claim 1 to comprise an isolated mammalian cell and thus to show the "hand of man" in its construction, rejection of claims 1-4 and 9 under 35

U.S.C. § 101 because the claimed invention is drawn to non-statutory subject matter, has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment of claim 1 to delete the definitive article "the", rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language has been withdrawn.

Claim Rejections - 35 USC § 102(b)

In view of Applicants' amendment of claim 1, rejection of claims 1, 2 and 4 under 35 U.S.C. 102(b) as being anticipated by Berlin et al. (US Patent 6,509,152, Date of Issue Jan. 21, 2003) has been withdrawn.

Berlin does not teach an isolated mammalian cell comprising a responsive transcription factor (RTF) selected from *Aspergillus nidulans* AlcR protein and a RTF derived from *Aspergillus nidulans* AlcR protein. Furthermore, Berlin does not teach a promoter or promoter fragments operatively linked to P_{alcA} operator sites as claimed specific for binding *Aspergillus nidulans* AlcR protein.

Claim Rejections - 35 USC § 103

In view of Applicants cancellation of claim 8, rejection of claims 1 and 8 under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) as applied to claims 1, 2, 5-7 and 9 above, and further in view of Smits et al., (2001, Plasmid, pp. 16-24, of record) is rendered moot.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 112- Second paragraph

In view of Applicants' amendment of claim 1 to recite at a cultivation temperature, rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language has been withdrawn.

Rejections maintained in response to Applicant arguments or amendments.

35 USC § 112- First paragraph- Written description

Claims 1-4, 9 remain rejected and claim 28 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In addition to the issues of enablement discussed in the previous office action filed on 04-29-2008, amended claims 1-4, 9 and claim 28 raise enabling issues in relation to a) a genus of RTF fragments/variants selected and derived from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% identical to the *Aspergillus nidulans* AlcR protein and b) a genus promoter fragments operatively linked to *A. nidulans* P_{AlcA} operator sites specific for *Aspergillus nidulans* AlcR protein, wherein said operator sites are

obtained by PCR amplification of the P_{AlcA} with the claimed primers specific exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde.

In the instant case, the specification teaches at page 5, the *Aspergillus nidulans* AlcR protein, which binds to the corresponding operator sequence as disclosed in GenBank accession No. S47331, nucleotides 30-308, in response to acetaldehyde (GenBank Accession No. S47331). The specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. There is no structure/function relationship taught at all for claimed genus of AlcR protein fragments with more than 90% homology to *Aspergillus nidulans* AlcR protein. There is no teaching of how many amino acid residues may be mutated and/or deleted that may affect binding to the operator sequence and AlcR-mediated transactivation in the presence of acetaldehyde.

The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). While one of skill in the art can readily envision numerable species of amino acid sequences that are at least a given % identity to a reference nucleotide sequence e.g., alcR gene (A) and that encode a polypeptide (e.g.,

Aspergillus nidulans AlcR protein) at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity.

Furthermore, Applicants have not sufficiently described other relevant identifying characteristics (e.g., binding domains in the *Aspergillus nidulans* AlcR protein), specific features and functional attributes (e.g *A. nidulans* AlcR-mediated transactivations in the presence of acetaldehyde) that would distinguish different members of the claimed genus. Although sufficient description is given for the full length of *Aspergillus nidulans* AlcR protein, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of a genus of unspecified fragments of RTF from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% homologous to the *Aspergillus nidulans* AlcR protein exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde, much less of any compound being gaseous. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Note that Applicant has not provided a response that properly applies to the rejection of claims 1-4, 9 and claim 28 under 35 U.S.C. 112, first paragraph, written description requirement, but has provided a single response that is equally relevant to rejections of claims under 35 U.S.C. 112, first paragraph, written description requirement, and scope of enablement. These are different rejections that merit separate responses as they pertain to different grounds of rejection. Please, note that the examiner's response to argument related to Applicant's traversal of

enablement rejection appear in the paragraph below under rejection Claim Rejections - 35 USC § 112 -scope of enablement.

Response to Applicants' arguments as they relate to rejection of claims 1-4, 9 and claim 28 under 35 USC § 112- First paragraph- Written description

In relation to the breadth of claim 1, subpart a, encompassing a genus of RTF fragments/variants selected and derived from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% identical to the *Aspergillus nidulans* AlcR protein, Applicants allege at pages 11-12 of Remarks, "The RTF is now restricted to the described and exemplified AIcR protein and AlcR protein derivatives. The AlcR derivatives as claimed in claim 1 are easy to prepare according to standard procedures and easy to test whether they fulfill the requirement of "which modulates transcription of operator-containing promoters in response ..., shown in the second half of part a. of claim 1". In addition, Applicants argue that " their preparation and testing is within the standard methods easily applied by the skilled person in the art. Applicants further note that they have now restricted part b. of claim 1 to the exemplified". Such is not persuasive.

The examiner refers applicants to the reasons already of record and the reasons explained in the paragraphs above. The specification mentions only the full length t the *Aspergillus nidulans* AlcR protein. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the fragments being more than 90% homologous to the *Aspergillus nidulans* AlcR protein exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde. The specification does not teach regions or domains of the protein that are essential for the

claimed activity. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. There is not structure/function relationship taught at all for the *Aspergillus nidulans* AlcR protein.

In relation to the claimed promoter fragments operatively linked to a P_{AlcA} operator sites specific for binding *Aspergillus nidulans* AlcR protein, applicants argue at page 12 of remarks that " they have now restricted part b. of claim 1 to the exemplified functional P_{AlcA} operator site as described in example 1 of the specification in order to expedite prosecution. Hence, the claims no longer encompass modified nucleotides (see page 6 of the Office Action, before quotation of 35 U.S.C. §112)". Such is not persuasive.

The instant claims are reading into any promoter fragment linked to P_{AlcA} operator sites specific for binding the *Aspergillus nidulans* AlcR protein domain amplified with primers identified with SEQ ID Nos. 1 and 2, with the contemplated functionality of exhibiting *A. nidulans* AlcR-mediated transactivation of a desired target gene in the presence of acetaldehyde. The specification discloses that a responsive promoter is designed by cloning the AlcR-specific OP site derived from the Aspergillus nidulans P_{AlcA} promoter 5' of a minimal version of the human cytomegalovirus immediate early promoter (US Pat. No. 5,464,758), which controls expression of the human placental secreted alkaline phosphatase SEAP (page 7, paragraph [042]) . Thus, the specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 of SEQ ID No. 1 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 of SEQ ID No. 2 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. Therefore, the specification does

not describe the claimed functional promoter fragments in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these peptides at the time of filing the present application. Thus, the written description requirement has not been satisfied.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 1-4 remain rejected, and claim 28 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) the responsive transcription factor (RTF) which is *Aspergillus nidulans* AlcR protein, and enabling for (b) a promoter operatively linked to a PCR-amplified promoter from a *A. nidulans* P_{AlcA} using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3' SEQ ID No. 1) and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3', SEQ ID No. 2) as forward and reverse primers,

does not provide an enabling disclosure for (a) a genus of RTF fragments selected and derived from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% identical to the *Aspergillus nidulans* AlcR protein. In addition, the specification does not provide sufficient guidance for (b) a genus promoter fragments operatively linked to *A. nidulans* P_{AlcA} operator sites specific for *Aspergillus nidulans* AlcR protein, wherein said operator sites are obtained by PCR amplification of the P_{AlcA} with the claimed specific primers said *Aspergillus nidulans* AlcR protein exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement

of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

In addition to the issues of enablement discussed in the previous office action filed on 04-29-2008, amended claims amended claims 1-4, 9 and dependent claim 28 raise enabling issues in relation to a) fragments and/or variants more than 90% homologous to *Aspergillus nidulans* AlcR protein able to bind to the corresponding operator sequence in an *A. nidulans* P_{alcA} promoter gene region as broadly claimed, so as to exhibit *A. nidulans* AlcR-mediated transactivation of a nuclei acid encoding a desired protein functionally linked to said promoter in the presence of acetaldehyde and b) any promoter fragment linked to P_{AlcA} operator sites specific for binding the *Aspergillus nidulans* AlcR protein domain amplified with primers identified with SEQ ID Nos. 1 and 2, with the contemplated functionality of exhibiting *A. nidulans* AlcR-mediated transactivation of a desired target gene in the presence of acetaldehyde.

The claims, when given the broadest possible interpretation, encompass a genus of unspecified fragments of RTF from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% homologous to the *Aspergillus nidulans* AlcR protein The specification provides insufficient data to enable claims directed to the fragments and/or variants of *Aspergillus nidulans* AlcR protein more than 90% homologous. Thereby, specific issues including the functional limitations of amino acid sequences of 90% homologous to the

Aspergillus nidulans AlcR protein that read on a genus of functional proteins able to bind to the corresponding operator sequence in an *A. nidulans* P_{alcA} promoter gene region so as to exhibit *A. nidulans* AlcR-mediated transactivation of a nuclei acid encoding a desired protein functionally linked to said promoter in the presence of acetaldehyde, have to be examined and considered for patentability regarding the broadly claimed RTF base sequences.

In the instant case, the specification teaches at page 5, the *Aspergillus nidulans* AlcR protein, which binds to the corresponding operator sequence as disclosed in GenBank accession No. S47331, nucleotides 30-308, in response to acetaldehyde (GenBank Accession No. S47331). The specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. There is no structure/function relationship taught at all for claimed genus of AlcR protein fragments with more than 90% homology to *Aspergillus nidulans* AlcR protein. There is no teaching of how many amino acid residues may be mutated and/or deleted that may affect binding to the operator sequence and AlcR-mediated transactivation in the presence of acetaldehyde.

The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007,

Science, pp. 525-528; p. 527, col. 3, last paragraph). While one of skill in the art can readily envision numerable species of amino acid sequences that are at least a given % identity to a reference nucleotide sequence e.g., alcR gene (A) and that encode a polypeptide (e.g., *Aspergillus nidulans* AlcR protein) at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein cannot be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a *Aspergillus nidulans* AlcR protein than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

Since it would require undue experimentation to identify other fragments and/or variants of *Aspergillus nidulans* AlcR protein other than the full length of *Aspergillus nidulans* AlcR protein, it certainty would require undue experimentation to make and use the invention as claimed. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of claimed fragments and/or variants of *Aspergillus nidulans* AlcR protein with more than 90% homology, able to exhibit responsive transcription factor-mediated transactivation in the presence of any compound being gaseous. As the result, given the unpredictability of the art and the lack of working example in the instant

specification, particularly when taken with the lack of guidance in the specification, it is incumbent upon the specification to disclose means for identifying such variants commensurate in scope with coverage sought by the claims.

Response to Applicants' arguments as they relate to rejection of claims 1-4, 9 and claim 28 under 35 USC § 112- First paragraph- Scope of enablement

In relation to the breadth of claim 1, subpart a, encompassing a genus of RTF fragments/variants selected and derived from *Aspergillus nidulans* AlcR protein comprising conservative substitutions and being more than 90% identical to the *Aspergillus nidulans* AlcR protein, Applicants allege at pages 11-12 of Remarks, "The RTF is now restricted to the described and exemplified AIcR protein and AlcR protein derivatives. The AlcR derivatives as claimed in claim 1 are easy to prepare according to standard procedures and easy to test whether they fulfill the requirement of "which modulates transcription of operator-containing promoters in response ..., shown in the second half of part a. of claim 1". In addition, Applicants argue that " their preparation and testing is within the standard methods easily applied by the skilled person in the art. Applicants further note that they have now restricted part b. of claim 1 to the exemplified". Such is not persuasive.

The examiner refers applicants to the reasons already of record and the reasons explained in the paragraphs above. The specification mentions only the full length t the *Aspergillus nidulans* AlcR protein. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the fragments being more than 90% homologous to the *Aspergillus nidulans* AlcR protein exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde.

The specification does not teach regions or domains of the protein that are essential for the claimed activity. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. Since it would require undue experimentation to identify other fragments and/or variants of *Aspergillus nidulans* AlcR protein other than the full length of *Aspergillus nidulans* AlcR protein, it certainty would require undue experimentation to make and use the invention as claimed. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of claimed fragments and/or variants of *Aspergillus nidulans* AlcR protein with more than 90% homology, able to exhibit responsive transcription factor-mediated transactivation in the presence of any compound being gaseous.

In relation to the claimed promoter fragments operatively linked to a P_{AlcA} operator sites specific for binding *Aspergillus nidulans* AlcR protein, applicants argue at page 12 of remarks that " they have now restricted part b. of claim 1 to the exemplified functional P_{AlcA} operator site as described in example 1 of the specification in order to expedite prosecution. Hence, the claims no longer encompass modified nucleotides (see page 6 of the Office Action, before quotation of 35 U.S.C. §112)". Such is not persuasive.

The instant claims are reading into any promoter fragment linked to P_{AlcA} operator sites specific for binding the *Aspergillus nidulans* AlcR protein domain amplified with primers identified with SEQ ID Nos. 1 and 2, with the contemplated functionality of exhibiting *A. nidulans* AlcR-mediated transactivation of a desired target gene in the presence of acetaldehyde. The specification discloses that a responsive promoter is designed by cloning the AlcR-specific OP site derived from the Aspergillus nidulans P_{AlcA} promoter 5' of a minimal version of the

human cytomegalovirus immediate early promoter (US Pat. No. 5,464,758), which controls expression of the human placental secreted alkaline phosphatase SEAP (page 7, paragraph [042]) . Thus, the specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 of SEQ ID No. 1 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 of SEQ ID No. 2 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. Hence it would require undue experimentation to determine alternative functional promoter fragment sequences meeting the claim requirements to exhibit *A. nidulans* AlcR-mediated transactivation of a desired target gene in the presence of acetaldehyde.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 9 remain rejected and claim 28 is newly rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record)

Response to Applicants' arguments as they relate to rejection of claims 1, 2, 4, 9 and 28 under 35 USC § 103

At page 13 of Remarks, in relation to the Caddick et al., publication, Applicants argue that Caddick et al., "describe the use of the ethanol-inducible AlcA/AlcR system in tobacco plant cells. This is a general teaching about the AlcA/AlcR system in plants". Moreover, Applicants allege that "the Office contends that a teaching directed towards AlcA/AlcR system in plants in combination with an inoperative suggestion in White that an ethanol-inducible AlcA/AlcR

system in mammalian cells renders obvious the claimed invention. Applicants respectfully disagree. The combination of these two references, as noted above, would not result in an operable system in mammalian cells because mammalian cells cannot utilize ethanol in an AlcA/AlcR system". Furthermore, Applicants contend that there is not teaching of the claimed "a responsive transcription factor derived from *Aspergillus nidulans* AlcR protein comprising the noted conserved amino acids and identity operably linked to P_{AlcA} operator obtained by amplifying with the noted oligonucleotides" [emphasis added] . Such is not persuasive.

Caddick et al., discloses a chemically-inducible plant gene expression cassette comprising a first promoter, e.g., the alcA gene promoter (i.e. the alcA gene encodes alcohol dehydrogenase I) operatively linked to a regulator sequence which encodes a regulator protein, e.g., the alcR regulator protein (e.g., responsive transcription factor), said alcR gene product induced in the presence of an effective exogenous inducer, i.e. by the protein/alcohol or protein/ketone combination. In response to applicant's argument that it would not have been obvious for one of ordinary skill in the art to combine the references as the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., ethanol does not induce the AlcA/AlcR system in mammalian cells is a general statement. Applicants have not have not provided probative evidence to support why ethanol-utilization in a mammalian cell would not activate AlcR. Indeed, the art at the effective fling date of the application, evidence that ethanol is metabolized to acetaldehyde in brain cells in culture, albeit less efficiently that in liver cells (Gonthier et al., 1997, Alcohol Clin Exp Res. pp. 1018-23; p.1018, col. 1, last paragraph). In addition, the use of prokaryotic transcriptional regulatory elements for controlled expression of cloned genes in mammalian cells and animals was well

known in the art as evidenced by the use of the *Streptomyces*-derived butyrolactone-responsive quorum-sensing systems to adjust transgene expression in mammalian cells and mice (Weber, 2003; Nucleic Acids Res. 2003 July 15; 31(14): e71) further supporting the use of the ethanol – inducible transgene expression Aspergillus nidulans AlcA/AlcR system in the White publication. Furthermore, as the alcR gene product taught by Caddick, which is induced by exogenous treatment with cyclohexanone (Example 5; col. 18, lines 55-58), exhibits transcription of the linked target gene, the alcA gene promoter necessarily contains the promoter domain from a *A. nidulans* P_{AlcA} generated by using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3' SEQ ID No. 1) and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3', SEQ ID No. 2) as forward and reverse primers, absent evidence to the contrary. White complements the teachings of Caddick by disclosing use of mammalian host cells to be transfected with an expression vector encoding the *Aspergillus nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters containing specific operator sites from *A. nidulans alcA* promoter. Moreover, White MRH discloses that vectors are introduced in mammalian cells and assay for luciferase reporter gene expression in the presence and absence of ethanol.

Claims 1 and 3 remain rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) as applied to claims 1, 2, 5-7 and 9 above, and further in view of Flipphi et al., (Bichem. J. 2002, pp. 25-31, of record).

Response to Applicants' arguments as they relate to rejection of claims 1 and 3 under

35 USC § 103

At page 14 of Remarks, in relation to the Flipphi et al., publication, Applicants argue that Flipphi et al., "describe isolation of AlcA and AlcR genes and show that the AlcA/AlcR system is inducible by several primary alcohols, primary monoamines and L-threonine, and corresponding aliphatic aldehydes. A skilled person in the art knowing Flipphi et al. and Craddick et al. and White would still not be guided to the instant invention, because there is no indication or hint how to construct the particular mammalian cell compromising AlcR protein or a derivative thereof and the particular PASTA operator site of part b. in amended claim 1".

The examiner refers applicants to the reasons already of record and the reasons as set forth and explained in the paragraphs above in relation to limitations (i.e., several primary alcohols, primary monoamines and L-threonine, and corresponding aliphatic aldehydes) are not recited in the rejected claim(s).

New grounds of rejection

Claim objection

Claim1 is objected to because of the following informalities: Applicants have amended claim 1, subpart a. to recite "at cultivation temperature". The phrase is grammatically incorrect as an indefinite article "a" is required in front of the claimed "cultivation temperature".

In addition, claim 1 objected to because at line 3 of the claim, the term "RTF" is preceded by the article "an" and not "a". Appropriate correction is requested.

Applicants have amended claim 1, subpart a. to recite "at cultivation temperature". The phrase is grammatically incorrect as an indefinite article "a" is required in front of the claimed "cultivation temperature". Appropriate correction is requested.

Amended claim 1 recites "an RTF derived from Aspergillus nidulans AlcR protein comprising conservative amino acid substitutions and being more than 90% identical to the Aspergillus nidulans AlcR protein". The metes and bounds of the term "derived" are indefinite because "derived" can encompass multiple meanings from the origin of something to deducing something. Therefore, the intended mean of the term, "derived" is vague and indefinite. Recitation of term "obtained or isolated from.." in place of derived would obviate the basis of this objection.

Furthermore, amended claim 1 is objected to for the inclusion of the nucleotide sequences identified as SEQ ID NO:1 and SEQ ID NO:2 in parenthesis. Sequence identifiers are the best description of the claimed sequence and thus should not be recited parenthetically.

In addition, claim 1 is objected to because of the recitation of both, the SEQ No identifier and the description of the nucleotide sequence. Recitation of just the SEQ No. would obviate the redundancy.

Other art for Comment

The following are cited to complete the record.

a) **Eysseric H**, et al., Characterization of the production of acetaldehyde by astrocytes in culture after ethanol exposure. Alcohol Clin Exp Res. 1997 Sep;21(6):1018-23.

b) **Weber** et al., *Streptomyces*-derived quorum-sensing systems engineered for adjustable transgene expression in mammalian cells and mice. Nucleic Acids Res. 2003 July 15; 31(14): e71.

Conclusion

Claims 1-4, 9 and 28 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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